II. REMARKS

Introductory Comments

Claims 1-7, 11-13 and 17-20 were examined in the Office Action under reply and stand variously rejected under (1) nonstatutory double patenting; and (2) 35 U.S.C. §103(a). These grounds of rejection are traversed for reasons discussed in detail below.

Applicant notes with appreciation the withdrawal of the previous rejections under 35 U.S.C. §102 and 35 U.S.C. §103.

Request for Rejoinder

Applicant reiterates the request that withdrawn claims 16 and 21, drawn to methods of using the compositions of elected Group I, be rejoined with the claims of Group I upon allowance of the product claims. This request was first presented prior to a final Office Action and prior to allowance of the application.

Rejections Over the Art

Claims 1-7, 11-13 and 17-20 were rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent Publication No. 2003/0180316 to Boutriau et al. ("Boutriau"), Kanra et al., *Pediatrics International* (2003) 45:314-318 ("Kanra") and Tauxe, R., *Emerging Infectious Disease* (2001) 7:516-521 ("Tauxe"). The Examiner asserts Boutriau teaches a multivalent vaccine conjugated to aluminum phosphate. The Office notes Boutriau does not teach the container labeling or a sealing process. Kanra allegedly teaches administration of DTaP plus Hib-CRM_{197} adjuvanted with $AlPO_4$. Tauxe is said to describe that the use of a hermetically sealed container such as a vial is a regular practice according to CDC regulations. However, applicant submits the claims indeed distinguish over the cited combination.

In particular, independent claim 1 and those claims dependent thereon are directed to a liquid combination vaccine. Boutriau discloses a combination vaccine that initially comprises two separate vaccines that become a liquid combination vaccine upon mixing. Applicant's vaccine differs from Boutriau in that it is always in liquid form ("full liquid"). Thus, the Hib conjugate is combined with the D, T and P components during

manufacture, and the combination is packaged and stored in a single container prior to use. The Boutriau vaccine, even after mixing, does not render the present claims obvious.

Boutriau teaches that the Hib conjugate is preferably **not** adsorbed onto aluminium salt adjuvant before being mixed with the DTPw vaccine (see, paragraph 0038). This statement implies that upon mixing the Hib conjugate with the DTPw vaccine, the Hib conjugate subsequently becomes adsorbed onto aluminium adjuvant salt. It is only after the mixing that the combination vaccine is present in a liquid form and therefore can be considered as fulfilling the initial "liquid combination vaccine" requirement of claim 1. However, in this liquid form, the vaccine does not fulfill all of the further requirements of claim 1. Claim 1 requires that the vaccine comprises an aluminium phosphate adjuvant but not an aluminium hydroxide adjuvant and that no more than 15% by weight of the Hib conjugate in the vaccine is adsorbed to aluminium phosphate. The DTPw-HepB vaccine (Tritanrix-HepB™ - see, example 1 of Boutriau) with which the Hib conjugate is mixed in Boutriau comprises both aluminium hydroxide and aluminium phosphate, and thus is directly contrary to applicant's claim 1. Even if the Hib conjugate in Boutriau might be mixed with a DTP vaccine that does not contain aluminium adjuvant, this combination still would not teach or suggest all of the elements of claim 1 because the most preferred Hib conjugate disclosed in Boutriau (see, paragraphs 0038-0040) contains no aluminium salt whatsoever, whereas applicant's claim 1 requires the vaccine to comprise aluminium phosphate adjuvant.

Thus, when the Boutriau reference is considered as a whole, as it must be, the skilled artisan would either consider producing a vaccine completely **devoid** of aluminium salts, or alternatively, they would have considered it necessary for a component of the vaccine (to which the Hib conjugate must be mixed in order to form the liquid combination vaccine) to contain **both** aluminium phosphate and aluminium hydroxide. It would not be obvious from a reading of Boutriau that a liquid combination vaccine could comprise aluminium phosphate (to which less than 15% by weight of the Hib conjugate is adsorbed) but not aluminium hydroxide.

Kanra and Tauxe do not provide the elements missing from Boutriau. First, although Kanra evaluates the safety and immunogenicity of the use of aluminium

phosphate with a Hib-CRM_{197} vaccine, Kanra does not teach or suggest the use of aluminium phosphate adjuvants for DTP vaccines. Thus, the combination of Boutriau and Kanra still leaves a DTP component with a mixture of aluminium phosphate and aluminium hydroxide. Nothing in the two references leads to a vaccine which includes aluminium phosphate but does **not** include aluminium hydroxide, let alone a vaccine in which no more than 15% by weight of the Hib conjugate is adsorbed to the aluminium phosphate. Tauxe does not even pertain to vaccines, but rather relates to food safety.

Based on the foregoing, it is apparent that independent claim 1 and those claims dependent thereon are not obvious over this combination and withdrawal of this basis for rejection is respectfully requested.

Similarly, independent claims 2-7 and those claims dependent thereon also distinguish over the combination of Boutriau, Kanra and Tauxe. In particular, claims 2-7 are directed to a "full liquid," i.e., a vaccine that is always in liquid form. As explained above, Boutriau's vaccine comprises two separate vaccines which are stored in separate containers in lyophilized form and is only converted to liquid form after mixing. This dual liquid/lyophilized format is an essential feature in Boutriau. See, e.g., Examples 2 and 4 and paragraph 0052 of Boutriau. In order for the two separate vaccines to be mixed together, the sealed vials in which they are stored must already be pierced when a liquid vaccine is made. Similarly, hermetic sealing is no longer intact when a liquid vaccine is made in Boutriau.

The Office suggests Tauxe teaches that the use of hermetically sealed containers is regular practice. Although sealing and labeling may have been known in the art, the key point here is the timing of these actions. Based on Boutriau, the skilled person will always have a lyophilized Hib component and will therefore never meet the requirements of claims 2-7. Kanra does not teach the elements missing from Boutriau and Tauxe as Kanra does not suggest the use of aluminium phosphate adjuvants for DTP vaccines. Accordingly, the cited combination fails to render the claims obvious and withdrawal of this basis for rejection is respectfully requested.

Claims 1-7, 11-13 and 17-20 were also rejected under 35 U.S.C. §103(a) as obvious over (1) Asensi et al, *Acta Paediatri* (2003) 92:541-545 ("Asensi"); (2) Gupta et al., *Biologicals* (1999) 27:167-176 ("Gupta") and (3) U.S. Patent No. 6,756,040 to

Peetermans et al. ("Peetermans"), each combined with Tauxe. However, applicant submits none of these combinations renders the instant claims obvious.

First, there is no suggestion in Asensi to use a vaccine in which the concentration of the Hib conjugate is less than 15 μg/ml and wherein no more than 15% by weight of the Hib conjugate is adsorbed to aluminium phosphate. Page 542, third paragraph of Asensi states that 10 μg/0.5 ml (i.e., 20 μg/ml) of Hib conjugate is used in the DTwPHib vaccine and that the Hib conjugate is "adsorbed onto aluminium phosphate." Although the exact percentage of the Hib conjugate adsorbed is not stated, the phrase "adsorbed onto aluminium phosphate" suggests that all, or substantially all, of the conjugate is adsorbed onto aluminium phosphate. This is certainly not a phrase that would be used to imply that only 15% or less of the Hib conjugate is adsorbed. In contrast, the claims substantially avoid adsorption of the Hib conjugate to aluminium phosphate. Tauxe does not provide the missing elements as Tauxe does not even pertain to vaccines, but rather relates to food safety. If one of skill in the art were to combine the teaching of Asensi with that of Tauxe, they would not arrive at the claimed subject matter. In fact, based on a reading of this combination, the skilled artisan would **not** have expected that the low dose of Hib conjugate, of which less than 15% by weight is adsorbed to aluminium phosphate, would provide a stable liquid DTP-Hib vaccine.

With respect to Gupta and Tauxe, Gupta discloses vaccine compositions in which antigens for protecting against diphtheria, tetanus, pertussis and Hib are used to form a single vaccine. However, all of the vaccine compositions mentioned in Gupta are adsorbed onto aluminium phosphate (see, Table 1 of Gupta). Therefore, in view of the teaching of Gupta, the skilled artisan would have considered it necessary for a combination vaccine including a Hib conjugate to be adsorbed to an aluminium adjuvant. Tauxe does not provide the elements missing from Gupta as Tauxe relates to food safety and not vaccine compositions. Thus, if the skilled person were to combine the teachings of Gupta and Tauxe, they would not arrive at the claimed invention.

Finally, Peetermans discloses a vaccine comprising a Hib conjugate that is adsorbed onto aluminium phosphate in order to overcome the reduction in antibody titres that normally occurs when the Hib component is mixed with other vaccine components (see, paragraphs 0005-0007). The concept that is central to Peetermans is that adsorbing

the Hib conjugate to aluminium phosphate allows the problems of mixing the Hib conjugate with other antigens to be overcome. Based on the teachings of this document, the skilled person certainly would not have considered that producing a vaccine in which less than 15% by weight of the Hib conjugate is adsorbed to aluminium phosphate would provide effective antibody levels. Thus, Peetermans teaches directly away from the claimed invention. Tauxe does not fill the gaps present in Peetermans as Tauxe does not pertain to vaccines, but rather relates to food safety.

Applicant submits the Examiner has chosen bits and pieces of the cited references in each of the combinations cited above to arrive at the allegation that these combinations of references suggest the claimed invention. This is improper. As stated in *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). Thus, a rejection cannot be predicated on the mere identification of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner.

For at least the above reasons, withdrawal of all of the rejections under 35 U.S.C. §103(a) is respectfully requested.

Nonstatutory Double Patenting

Claims 1, 4, 8, 9, 10 and 12[1] were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12-17 of U.S. Application Serial No. 11/886,556. Applicant notes this rejection is provisional and hence premature as the purported conflicting claims have not in fact been patented and it is unclear at this time the ultimate claims that will be allowed. Accordingly, applicant reiterates the request to hold the rejection in abeyance until

[1] Applicant notes claims 8-10 were previously canceled.

allowable subject matter is indicated in this application. Applicant will then consider the propriety of filing a Terminal Disclaimer.

III. CONCLUSION

Applicant respectfully submits that the claims are now in condition for allowance and request early notification to that effect. The Examiner is encouraged to contact the undersigned if the Examiner notes any further matters which might be resolved by a telephone interview.

Respectfully submitted,

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By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440